

## PATENT COOPERATION TREATY

PCT

## NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

United States Patent and Trademark  
Office  
(Box PCT)  
Crystal Plaza 2  
Washington, DC 20231  
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

<b>Date of mailing</b> (day/month/year) 12 June 1997 (12.06.97)	
<b>International application No.</b> PCT/IL96/00143	<b>Applicant's or agent's file reference</b> 3/130/63-PCT
<b>International filing date</b> (day/month/year) 06 November 1996 (06.11.96)	<b>Priority date</b> (day/month/year) 06 November 1995 (06.11.95)
<b>Applicant</b> SANDALON, Ziv et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:

23 May 1997 (23.05.97)

☐ in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was  
☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

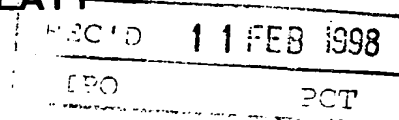
<p>The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland</p> <p>Facsimile No.: (41-22) 740.14.35</p>	<p>Authorized officer</p> <p>Marie-José Devillard</p> <p>Telephone No.: (41-22) 338.83.38</p>
--	---

# PATENT COOPERATION TREATY

## PCT

### INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)





Applicant's or agent's file reference 3/130/63-PCT	<b>FOR FURTHER ACTION</b>		See Notification of Transmittal of International Preliminary Examination Report (PCT/IPEA/416)
International application No. PCT/IL96/00143	International filing date (day/month/year) 06/11/1996	Priority date (day/month/year) 06/11/1995	
International Patent Classification (IPC) or national classification and IPC C12N15/86			
Applicant YISSUM RESEARCH DEVELOPMENT COMPANY ... et al.			

- This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
- This REPORT consists of a total of 10 sheets, including this cover sheet.  
  
☒ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).  
  
 These annexes consist of a total of 8 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☒ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand  23/05/1997	Date of completion of this report  09.02.98
Name and mailing address of the IPEA/   European Patent Office D-80298 Munich Tel. (+49-89) 2399-0. Tx: 523656 epmu d Fax: (+49-89) 2399-4465	Authorized officer  Pilat, D  Telephone No. (+49-89) 2399-8668  

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/IL96/00143

**I. Basis of the report**

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

**Description, pages:**

1-34 as originally filed

**Claims, No.:**

1-48 as received on 20/01/1998 with letter of 13/01/1998

**Drawings, sheets:**

1/6-6/6 as originally filed

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:  
☐ the claims, Nos.:  
☐ the drawings, sheets:

3. ☒ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

**see separate sheet**

4. Additional observations, if necessary:

**III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application.  
☒ claims Nos. 45.46.

because:

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/IL96/00143

- ☒ the said international application, or the said claims Nos. 45,46 relate to the following subject matter which does not require an international preliminary examination (*specify*):

**see separate sheet**

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☐ no international search report has been established for the said claims Nos. .

## IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

- ☐ restricted the claims.
- ☐ paid additional fees.
- ☐ paid additional fees under protest.
- ☒ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

- ☐ complied with.
- ☒ not complied with for the following reasons:

**see separate sheet**

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

- ☐ all parts.
- ☒ the parts relating to claims Nos. paragraph 1.1 item i).

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/IL96/00143

## V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

### 1. Statement

Novelty (N)	Yes:	Claims	9,16,17,27,33,34,42,44
	No:	Claims	1-8,13,18,20-22,24-26,35,37-38,41,43,45-48
Inventive step (IS)	Yes:	Claims	
	No:	Claims	9,16,17,27,33,34,42,44
Industrial applicability (IA)	Yes:	Claims	1-9,13,16-22,24-27,33-38,41,44,47,48
	No:	Claims	

### 2. Citations and explanations

**see separate sheet**

## VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

**see separate sheet**

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

---

International application No. PCT/IL96/00143

Reference is made to the following documents:

D1: WO-A-9216638

D2: PNAS USA vol.83, September, 1986, p.6925-29, Oppenheim A. et al.

**1) Unity (Article 34 (3)(a) and Rules 13, 68 PCT)**

The application lacks unity within the meaning of article 34 (3)(a) and Rules 13, 68 PCT for the following reasons:

**1.1 The following inventions have been identified:**

A construct capable of infecting a mammalian cell comprising at least one semi-purified (or pure) SV40 capsid protein; and a therapeutic constituent, wherein said therapeutic constituent is either:

i) an exogenous DNA and the methods and applications thereof (see claims 1-9,13,16-22,24-27,33-38,41-48 partially).

ii) an exogenous RNA and the methods and applications thereof (see claims 1-11,13-21,23-24,28,33-48 partially).

iii) an exogenous protein and the methods and applications thereof (see claims 1-9,12,16,17,29-34,41-48 partially).

**1.2) The common concept linking together the subject-matter of i) to iii) is the following:**

A construct capable of infecting a mammalian cell comprising at least one semi-purified, which comprises the option of being pure, SV40 capsid protein and a therapeutic constituent.

**1.3) D1 discloses a transduction vehicle which comprises SV40 capsid proteins, VP1 to VP3 (see, D1, p.6, lines 17-22 and example 1 p.21-23), which are purified (see D1, p.24, paragraph E) and a nucleoprotein complex (see D1, p.24-25**

paragraph III and IV). The nucleoprotein contains a double stranded DNA molecule enclosed within the capsid, said DNA containing a non-viral DNA (see D1, p.3, lines 20-29; p.4, lines 19-29; p.7-8, lines 27-2 and p.25 paragraph III). Said vehicle has been shown to be infectious (D1, p.27 paragraph VI). Furthermore, D1 discloses that the non viral DNA of the vehicle may encode for proteins that will protect a person or animal from infective cells or viruses and that the vehicle may be used against cancers by correcting the gene defect or to repress the unwanted gene expression. Finally, gene therapy vectors may be engineered to replace defective genes, to properly control gene expression or to encode a functional protein. In all the above areas the vehicle represents a means for gene therapy (see D1, "Uses for the vehicle" p.17-20).

In view of the teaching of D1 it is implicit that the vehicle described in D1 would comprise a plasmid which encodes a therapeutic constituent or therapeutic constituent itself when it has to be used for gene therapy (an exogenous DNA encoding a therapeutic exogenous protein or encoding therapeutic RNA or itself a therapeutic product). Thus, claim 1 is not new.

- 1.4 Hence the Examining Division considers that these separate inventions or groups of inventions are not so linked as to form a single general inventive concept.
- 1.5) Moreover, it cannot be excluded that any of the subject-matter identified above does not meet the requirements of Article 34 (3)(a) and Rules 13 and 68 PCT, a posteriori. The applicant should therefore be aware of a possible objection based on lack of unity in any regional phase of the present application.

## **2) Amendments (Article 19/34 PCT)**

The amended claims 18 and 35 introduce subject-matter which extends beyond the content of the application as filed and therefore infringe Article 34(2)(b) PCT. The amendments concerned are the following:

" a method for the *in vitro* construction of SV40 viruses or pseudoviruses comprising exogenous nucleic acid comprising the following steps:

- a) allowing a semi-purified or pure SV40 capsid protein or a mixture of at least two such proteins to self-assemble into SV40-like particles and
- b) bringing the SV40-like particles assembled in step a) into contact with said exogenous nucleic acid to give recombinant.

No basis in the application as filed has been identified which describes a method allowing semi-purified or pure SV40 capsid proteins to self-assemble into SV-40 like particles and bringing said SV40-like particles assembled in the first step into contact with said exogenous nucleic acid ... . Throughout the present application the method of in vitro construction comprises the steps of bringing a semi-purified or pure SV40 capsid protein ... into contact with the exogenous nucleic acid (see present description p.6, 4th paragraph; p.8, 1st paragraph; p.16, 3rd paragraph; p.18, 3rd paragraph; p.24 last paragraph, p.26, lines 18-21, p.27, lines 4-8). There is no indication for a first step of self assembly of semi-purified or pure SV40 capsid proteins into SV40-like particles which is then followed by a contact of the self-assembled particle to the nucleic acid.

### **3) Novelty (Article 33 (2) PCT)**

- 3.1) D1 discloses a transduction vehicle which comprises SV40 capsid proteins, VP1 to VP3 (see D1, p.6, lines 17-22 and example 1 p.21-23), which are purified (see D1, p.24, paragraph E) and a nucleoprotein complex (see D1, p.24-25 paragraph III and IV). The nucleoprotein contains a double stranded DNA molecule enclosed within the capsid, said DNA containing a non-viral DNA (see D1, p.3, lines 20-29; p.4, lines 19-29; p.7-8, lines 27-2 and p.25 paragraph III). Said vehicle has been shown to be infectious (D1, p.27 paragraph VI). Furthermore, D1 discloses that the non viral DNA of the vehicle may encode for proteins that will protect a person or animal from infective cells or viruses and that the vehicle may be used against cancers by correcting the gene defect or to repress the unwanted gene expression. Finally, gene therapy vectors may be engineered to replace defective genes, to properly control gene expression or to encode a functional protein. In all the above areas the vehicle represents a means for

gene therapy (see D1, "Uses for the vehicle" p.17-20).

In view of the teaching of D1 it is implicit that the vehicle described in D1 would comprise a plasmid which encodes a therapeutic constituent or therapeutic constituent itself when it has to be used for gene therapy (an exogenous DNA encoding a therapeutic exogenous protein or encoding therapeutic RNA or itself a therapeutic product).

Moreover, said non viral DNA may be a regulatory nucleotide or may code for enzymes, hormones, neurotransmitter, antibodies, structural proteins, repressor proteins and operator proteins (see D1, p. 7-8 bridging paragraph). The further selection of a DNA as an antisense DNA that react with messenger RNA or DNA is not new either (see D1, p.17, first paragraph). Thus, claims 1 to 8 and 13 lack novelty.

- 3.2) D1 discloses a method which comprises 1) synthesizing SV40 viral capsid proteins in cells, 2) allowing the nucleoprotein complex to come into contact with said viral capsid proteins (VP1 to VP3) to form a capsid enclosing said nucleoprotein complex, said nucleoprotein containing a double stranded DNA molecule comprising a nonviral DNA. (see D1, p.3, lines 20-29 and p.4, lines 19-29 and example 1 p.21-27). Accordingly, claims 18, 20-22 are not new.
- 3.3) The dependent claims 24-26 which refer to a method using an exogenous DNA encoding a therapeutic protein has already been disclosed (see D1, p.4 lines 21-29, p.7-8 lines 27-2 and p.17-19). Therefore, claims 24-26 are not new.
- 3.4) The method of claim 34 wherein the constituent is a DNA which encodes proteins or an antisense DNA that interfere with the replication or other functions has already been disclosed (see D1, p.17 lines 1-8 and lines 28-29 and p.18, lines 14-25). Consequently, the methods of claims 35, 37-38 lack novelty.
- 3.5) D1 discloses a mammalian cell (CV-1) infected with a transduction vehicle (see D1, p.27-28 paragraph VI and VII). Consequently, claims 41 and 43 lack novelty.
- 3.6) A method of providing a therapeutic DNA by means of such transduction vehicles has been disclosed in document D1 (see, p.17-19 and p.20 lines 14-

24). Similarly, D1 discloses also the provision of cells infected by said vehicle as therapeutic means (see p.20 lines 1-10). Accordingly, the pharmaceutically composition comprising a therapeutically effective amount of SV40 or infected cells are known. Therefore, claims 45 to 48 are not novel.

**4) Inventive step (Article 33 (3) PCT)**

- 4.1) The choice to include in the construct an SV40 derived *ori* DNA as described in claim 9 is a mere choice the skilled man would have performed according to the circumstances. He would for example have used a vector with an SV40 origin of replication (*ori*) to facilitate the replication of the plasmid in COS cells (see D2, abstract, lines 10-13). Therefore, claim 9 lacks an inventive step. The same objection applies to the use of such a construct in the method of claim 27.
- 4.2) The choice to use specific human cells which are infected by the transduction vehicle as described in the dependent claims 16-17 or to select specific human cells to be transformed by a known method is a mere choice the skilled man would have performed according to the circumstances. For an optimum effect for example, he would obviously select the most appropriate cells for the expression of said therapeutic product. Therefore, the selection of the human cells claimed in claims 16-17 and 33-34 does not involve an inventive step. The same objection applies to the infected human cell of 42 and 44.
- 4.3) The choice to add an additional step of nuclease digestion in a known method is a mere choice the skilled man would have performed in order to obtain a clean solution of DNA packaged particles. Since, this additional step is known in the art and has been used for polyoma capsid (see D1, p.2 lines 5-9), the addition of said step to a known method (see point 3.2 above) lacks an inventive step. As a consequence, claims 19 and 36 are obvious.

**5) Industrial applicability (Article 33 (4) PCT)**

According to Rule 67.1(iv), the International Preliminary Examination Authority, in the present case the EPO, is not required to carry out an international preliminary examination if the subject-matter of the international application

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

---

International application No. PCT/IL96/00143

relates to methods of treatment of the human or animal body by surgery or therapy, as well as diagnostic methods. The methods defined in claims 45, 46 are methods of treatment of the human body or animal body and thus no international examination concerning industrial applicability has been performed for these claims.

A set of the amended claims with the marked revisions, filed with response to the Written Opinion. Added matter is underlined. Deleted matter is square-bracketed.

**CLAIMS:**

1. A construct capable of infecting a mammalian cell comprising  
at least one semi-purified or pure SV40 capsid protein; and  
a constituent selected from the group consisting of
  - an exogenous DNA encoding a[n] therapeutic exogenous protein or peptide product, or encoding therapeutic RNA, or itself a therapeutic product,
  - a vector comprising an exogenous DNA encoding a[n] therapeutic exogenous protein or peptide product, or encoding therapeutic RNA, or itself a therapeutic product,
  - an exogenous RNA encoding a[n] therapeutic exogenous protein or peptide product or itself a therapeutic product,
  - a vector comprising an exogenous RNA encoding a[n] therapeutic exogenous protein or peptide product or itself a therapeutic product,
  - a[n] therapeutic exogenous protein or peptide product, and
  - antisense RNA, ribozyme RNA or any RNA or DNA which inhibits or prevents the expression of undesired protein/s in said mammalian cell; and  
[optionally] further comprising operatively linked regulatory elements sufficient for the expression and/or replication of said exogenous protein in a mammalian cell.
2. A construct according to claim 1 [optionally] further comprising additional SV40 protein or proteins, preferably SV40 agnoprotein.
3. A construct according to claim 1 or claim 2 comprising a mixture of at least two semi-purified or pure SV40 capsid proteins.
4. A construct according to any one of claims 1 to 3 comprising a mixture of three semi-purified or pure SV40 capsid proteins.

5. A construct according to claim 1 to 4 wherein said SV40 capsid protein is semi-purified or pure VP1 or VP2 or VP3.
6. A construct according to any one of claims 1 to 5 wherein said constituent is exogenous circular or linear DNA encoding a[n] therapeutic exogenous protein or peptide product, or itself a therapeutic product, or encoding therapeutic RNA, or a vector comprising exogenous DNA encoding therapeutic RNA or encoding a[n] therapeutic exogenous protein or peptide product.
7. A construct according to claim 6 wherein said DNA is DNA which encodes a therapeutic protein or peptide product which is not made or contained in said cell, or is DNA which encodes a therapeutic protein or peptide product which is made or contained in said cell in abnormally low amount, or is DNA which encodes a therapeutic protein or peptide product which is made or contained in said cell in defective form or is DNA which encodes a therapeutic protein or peptide product which is made or contained in said cell in physiologically abnormal or normal amount, or encodes a therapeutic RNA.
8. A construct according to claim 6 or claim 7 wherein said therapeutic protein or peptide product is an enzyme, a receptor, a structural protein, a regulatory protein or a hormone.
9. A construct according to any one of claims 6 to 8 comprising SV40-derived *ori* DNA sequence as a replication regulatory element and further comprising a DNA sequence encoding one or more regulatory elements sufficient for the expression of said exogenous RNA or exogenous protein or peptide in said mammalian cell.
10. A construct according to any one of claims 1 to 5 wherein said constituent is exogenous RNA, wherein said RNA is RNA which encodes a therapeutic protein or peptide product which is not made or contained in said cell, or is RNA which encodes a therapeutic protein or peptide product which is made or contained in said cell in abnormally low amount, or is RNA which encodes a therapeutic protein or peptide product which is made contained in said cell

in defective form, or is RNA which encodes a therapeutic protein or peptide product which is made or contained in said cell in physiologically abnormal or normal amount, said RNA having regulatory elements, including translation signal/s sufficient for the translation of said protein or peptide product in said mammalian cell, operatively linked thereto.

11. A construct according to claim 10 wherein said therapeutic protein or peptide product is an enzyme, a receptor, a structural protein, a regulatory protein or a hormone.

[12. A construct according to any one of claims 1 to 5 wherein said constituent is an exogenous protein or peptide product.]

12. A construct according to any one of claims 1 to 5 [12] wherein said constituent is a therapeutic exogenous protein or peptide product which is, respectively, a therapeutic protein or peptide product which is not made or contained in said cell, or is a therapeutic protein or peptide product which is made or contained in said cell in abnormally low amount, or is a therapeutic protein or peptide product which is made or contained in said cell in defective form or is a therapeutic protein or peptide product which is made or contained in said cell in physiologically abnormal or normal amount.

13. A construct according to any one of claims 1 to 5 wherein said constituent is antisense RNA or DNA or ribozyme RNA, or any RNA or DNA which inhibits or prevents the expression of undesired protein/s in said mammalian cell.

14. A construct according to claim 13 wherein said antisense RNA is antisense RNA directed against the *bcr/abl* transcript.

15. A construct according to claim 13 wherein said antisense RNA is antisense RNA directed against a HIV transcript.

16. A construct according to any one of the preceding claims wherein said cell is a human cell selected from the group consisting of hemopoietic cells, epithelial

cells, endothelial cells, liver cells, epidermal cells, muscle cells, tumor cells, nerve cells and germ line cells.

17. A construct according to claim 16 wherein said hemopoietic cells are bone marrow cells, peripheral blood cells and cord blood cells, or liver cells.
18. A method for the *in vitro* construction of SV40 viruses or pseudoviruses comprising exogenous nucleic acid comprising the following steps:
  - a. [bringing] allowing a semi-purified or pure SV40 capsid protein or a mixture of at least two such proteins to self-assemble into SV40-like particles; and
  - b. bringing the SV40-like particles assembled in step (a) into contact with said exogenous nucleic acid to give recombinant SV40 viruses or with a vector comprising said exogenous nucleic acid to give pseudoviruses. [and
  - b. optionally subjecting the SV40 viruses or pseudoviruses formed in step (a) to digestion by nuclease to remove non-packaged DNA.]
19. The method of claim 18 wherein said recombinant SV40 viruses or pseudoviruses are subjected to digestion by nuclease to remove non-packaged DNA.
20. A method according to claim 18 or 19 wherein in step (a) at least one other SV40 protein, preferably SV40 agnoprotein, is added to the mixture of said SV40 capsid protein/s and said nucleic acid.
21. A method according to any one of claims 18 to 20 wherein said SV40 capsid protein is semi-purified or pure SV40 VP1, VP2, or VP3.
22. A method according to any one of claims 18 to 21 wherein said exogenous nucleic acid is circular or linear DNA.
23. A method according to any one of claims 18 to 21 wherein said exogenous nucleic acid is RNA.

24. A method according to any one of claims 18 to 23 wherein said exogenous nucleic acid encodes a therapeutic protein or peptide product or itself a therapeutic product.
25. A method according to claim 22 wherein said DNA is DNA which encodes a therapeutic protein or peptide product which is not made or contained in said cell, or is DNA which encodes a therapeutic protein or peptide product which is made or contained in said cell in abnormally low amount, or is DNA which encodes a therapeutic protein or peptide product which is made or contained in said cell in defective form or is DNA which encodes a therapeutic protein or peptide product which is made or contained in said cell in physiologically abnormal or normal amount or is DNA which encodes a therapeutic RNA.
26. A method according to claim 25 wherein said exogenous DNA encodes a therapeutic protein or peptide product which is an enzyme, a receptor, a structural protein, a regulatory protein or a hormone.
27. A method according to any one of claims 18 to 20 wherein in step (b) SV40-derived *ori* DNA sequence is added and said exogenous nucleic acid [optionally] has DNA sequence encoding one or more regulatory elements sufficient for the expression of said exogenous protein in said mammalian cell operatively linked thereto.
28. A method according to any one of claims 18 to 20 wherein said nucleic acid is exogenous RNA, wherein said RNA is RNA which encodes a therapeutic protein or peptide product which is not made or contained in said cell, or is RNA which encodes a therapeutic protein or peptide product which is made or contained in said cell in abnormally low amount, or is RNA which encodes a therapeutic protein or peptide product which is made or contained in said cell in defective form or is RNA which encodes a therapeutic protein or peptide product which is made or contained in said cell in physiologically abnormal or normal amount and wherein said RNA has regulatory elements, including translation signal, sufficient for the translation of said protein product in said mammalian cell, operatively linked thereto.

PUBLISHED SHEET

29. A method for the *in vitro* construction of recombinant SV40 viruses or pseudoviruses comprising an exogenous therapeutic protein or peptide comprising the following steps:
- a. [bringing] allowing a semi-purified or purified SV40 capsid protein or a mixture of at least two such proteins to self-assemble into SV40-like particles; and
  - b. bringing the SV40-like particles assembled in step (a) into contact with said exogenous protein to give recombinant SV40 viruses or pseudoviruses. [and
  - b. optionally purifying the recombinant viruses or pseudoviruses obtained in step (a) from any non-packaged protein.]
30. A method according to claim 29 wherein said recombinant SV40 viruses or pseudoviruses are purified from any non-packaged protein.
31. A method according to claim 29 or claim 30 wherein said exogenous protein or peptide are, respectively, a naturally occurring or recombinant protein or peptide, a chemically modified protein or peptide, or a synthetic protein or peptide.
32. A method according to claim 31 wherein said exogenous protein or peptide product are, respectively, a therapeutic protein or peptide product not made or contained in said cell, or are a therapeutic protein or peptide product made or contained in said cell in abnormally low amount, or are a therapeutic protein or peptide product made or contained in said cell in defective form or are a therapeutic protein or peptide product made or contained in said cell in physiologically abnormal or normal amount.
33. A method according to any one of claims 18 to 32 wherein said cell is a human cell selected from the group consisting of hemopoietic cells, muscle cells, tumor cells, nerve cells and germ line cells.
34. A method according to claim 33 wherein said hemopoietic cells are bone marrow cells, peripheral blood cells and cord blood cells, or liver cells.

35. A method for the *in vitro* construction of SV40 pseudoviruses comprising exogenous antisense RNA, or ribozyme RNA or RNA or DNA which inhibits or prevents the expression of undesired protein/s in a mammalian cell, comprising the following steps:
- a. [bringing] allowing a semi-purified or pure SV40 capsid protein or a mixture of at least two such proteins to self assemble into SV40-like particles; and
  - b. bringing said SV40-like particles obtained in step (a) into contact with said exogenous antisense RNA, or ribozyme RNA, or RNA or DNA which inhibits or prevents the expression of undesired protein/s in a mammalian cell, to give recombinant SV40 pseudoviruses. [and
  - b. optionally subjecting the SV40 pseudoviruses formed in step (a) to digestion by nuclease to remove non-packaged DNA.]
36. The method of claim 35 wherein said pseudoviruses are subjected to digestion by nuclease to remove non-packaged DNA.
37. A method according to claim 35 or 36 wherein in step (a) at least one other SV40 protein, preferably SV40 agnoprotein, is added to the mixture of SV40 capsid protein/s and the exogenous nucleic acid or antisense nucleic acid.
38. A method according to any one of claims 35 to 37 wherein said SV40 capsid protein is semi-purified or pure SV40 VP1, VP2, or VP3.
39. A method according to any one of claims 35 to 38 wherein said antisense RNA is antisense RNA directed against the *bcr/abl* transcript.
40. A method according to any one of claims 35 to 38 wherein said antisense RNA is antisense RNA directed against a HIV transcript.
41. A mammalian cell infected with a construct of any one of claims 1 to 17.
42. An infected human cell according to claim 41 selected from the group consisting of hemopoietic cells, muscle cells, tumor cells, nerve cells and germ line cells.

43. A mammalian cell infected with a construct obtained by the method of any one of claim 18 to 40.
44. An infected human cell according to claim 43 selected from the group consisting of hemopoietic cells, muscle cells, tumor cells, nerve cells and germ line cells.
45. A method of providing a therapeutic DNA, RNA, antisense RNA, ribozyme RNA, protein or peptide product to a patient in need of such product by administering to said patient a therapeutically effective amount of the SV40 viruses or pseudoviruses according to any one of claims 1 to 17.
46. A method of providing a therapeutic DNA, RNA, antisense RNA, ribozyme RNA, protein or peptide product to a patient in need of such product by administering to said patient a therapeutically effective amount of infected cells according to any one of claims 41 to 44.
47. Pharmaceutical compositions comprising as active ingredient a therapeutically effective amount of the SV40 viruses or pseudoviruses according to any one of claims 1 to 17.
48. Pharmaceutically compositions comprising as active ingredient a therapeutically effective amount of infected cells according to any one of claims 41 to claim 44.

RECEIVED  
JAN 10 1964



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification:</b> <b>C12N 15/86, 15/87, 15/37, 7/04, 5/10,</b> <b>C07K 14/025, A61K 39/12, 48/00</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 97/17456</b>  <b>(43) International Publication Date:</b> 15 May 1997 (15.05.97)
<b>(21) International Application Number:</b> PCT/IL96/00143  <b>(22) International Filing Date:</b> 6 November 1996 (06.11.96)  <b>(30) Priority Data:</b> 115880                      6 November 1995 (06.11.95)                      IL  <b>(71) Applicants (for all designated States except US):</b> YISSUM RESEARCH DEVELOPMENT COMPANY OF THE HEBREW UNIVERSITY OF JERUSALEM [IL/IL]; P.O. Box 4279, 91042 Jerusalem (IL). HADASIT MEDICAL RESEARCH SERVICES AND DEVELOPMENT COMPANY LTD. [IL/IL]; P.O. Box 12000, 91120 Jerusalem (IL).  <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> SANDALON, Ziv [IL/IL]; 13 Yahud Street, 49360 Petach Tikva (IL), OPPENHEIM, Amos, B. [IL/IL]; 5 Harav Schrem Street, 96920 Jerusalem (IL). OPPENHEIM, Ariella [IL/IL]; 5 Harav Schrem Street, 96920 Jerusalem (IL).  <b>(74) Agent:</b> HACKMEY, Michal; A.E. Mulford, P.O. Box 544, 91004 Jerusalem (IL).		<b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
<b>(54) Title:</b> IN VITRO CONSTRUCTION OF SV40 VIRUSES AND PSEDOVIRUSES		
<b>(57) Abstract</b>  <p>The invention relates to constructs capable of infecting mammalian cells comprising at least one semi-purified or pure SV40 capsid protein and a constituent selected from the group consisting of an exogenous DNA, a vector comprising an exogenous DNA, an exogenous RNA, a vector comprising an exogenous RNA, an exogenous protein or peptide product, and antisense RNA, ribozyme RNA or any RNA or DNA which inhibits or prevents the expression of undesired protein(s) in said mammalian cell and optionally further comprising operatively linked regulatory elements sufficient for the expression and/or replication of said exogenous protein in a mammalian cell. The protein product is preferably a therapeutic protein or peptide product which is not made or contained in mammalian cells, or is made or contained in such cells in abnormally low amount, or is made or contained in such cells in defective form, or is made or contained in mammalian cells in physiologically abnormal or normal amount and can be an enzyme, a receptor, a structural protein, a regulatory protein or a hormone. The invention further relates to a method for the <i>in vitro</i> construction of SV40 viruses or pseudoviruses constructs according to the invention. In a further aspect, the invention relates to mammalian, preferably human cells infected with the constructs of the invention or with constructs obtained by any of the methods of the invention. Still further, the invention relates to a method of providing a therapeutic DNA, RNA, protein or peptide product or antisense RNA to a patient in need of such product by administering to the patient a therapeutically effective amount of the SV40 viruses or pseudoviruses of the invention or a therapeutically effective amount of infected cells according to the invention. Pharmaceutical compositions comprising as active ingredient a therapeutically effective amount of the SV40 viruses or pseudoviruses according to the invention or a therapeutically effective amount of infected cells according to the invention are also within scope of this application.</p>		

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/IL 96/00143

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C12N15/86 C12N15/87 C12N15/37 C12N7/04 C12N5/10  
C07K14/025 A61K39/12 A61K48/00

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07K C12N A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JOURNAL OF VIROLOGY, vol. 67, no. 5, May 1993, pages 2779-2788, XP000645492 COLOMAR M. ET AL.: "Opening and refolding of Simian Virus 40 and in vitro packaging of foreign DNA" cited in the application see the whole document ---	1-6, 19-22, 39,41
X	WO 92 16638 A (PRIME 3 PRIME INC 5) 1 October 1992  see the whole document ---	1-8,12, 13, 17-22, 24-26, 29,33, 39,41, 43-46
	-/-	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \* & \* document member of the same patent family

Date of the actual completion of the international search

14 March 1997

Date of mailing of the international search report

25.03.97

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (- 31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (- 31-70) 340-3016

Authorized officer

Kania, T

# INTERNATIONAL SEARCH REPORT

Patent Application No

PCT/IL 96/00143

**C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>HUMAN GENE THERAPY, vol. 6, no. 3, March 1995, pages 297-306, XP000645479 FORSTOVA, J. ET AL.: "Polyoma virus pseudocapsids as efficient carriers of heterologous DNA into mammalian cells" cited in the application see the whole document ---</p>	1-46
A	<p>PNAS, U.S.A., vol. 83, September 1986, pages 6925-6929, XP002027487 OPPENHEIM A. ET AL.: "Efficient introduction of plasmid DNA into human hemopoietic cells by encapsidation in Simian Virus 40 pseudovirions" cited in the application see the whole document ---</p>	1-46
A	<p>VIROLOGY, vol. 207, no. 1, 20 February 1995, pages 251-254, XP002027488 GHARAKHANIAN E. ET AL.: "SV40 VP1 assembles into disulfide-linked postpentameric complexes in cell-free lysates" see the whole document ---</p>	1-46
A	<p>SCIENCE, vol. 253, 2 August 1991, pages 562-565, XP002027489 SZCZYLIK C. ET AL.: "Selective inhibition of leukemia cell proliferation by bcr-abl antisense oligodeoxynucleotides" cited in the application see the whole document ---</p>	15,37
T	<p>BLOOD, vol. 88, no. 10, 15 November 1996, page 3903 XP000647476 SANDALON Z. ET AL.: "In vitro packaging of SV40 virions and pseudovirions: vector development for somatic gene therapy" see the whole document -----</p>	1-46

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/IL 96/00143

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 43, 44  
because they relate to subject matter not required to be searched by this Authority, namely:  
Remark: Although claims 43, 44 (as far as in vivo methods are concerned) are directed to a method of treatment of (diagnostic method practised on) the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

### Information on patent family members

Technical Application No

PCT/IL 96/00143

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9216638 A	01-10-92	NONE	

**CLAIMS:**

1. A construct capable of infecting a mammalian cell comprising  
at least one semi-purified or pure SV40 capsid protein; and  
5 a constituent selected from the group consisting of
- an exogenous DNA encoding an exogenous protein or peptide product, or encoding therapeutic RNA, or itself a therapeutic product,
  - a vector comprising an exogenous DNA encoding an exogenous protein or peptide product, or encoding therapeutic RNA, or itself a therapeutic product,  
10
  - an exogenous RNA encoding an exogenous protein or peptide product or itself a therapeutic product,
  - a vector comprising an exogenous RNA encoding an exogenous protein or peptide product or itself a therapeutic product,
  - 15 - an exogenous protein or peptide product, and
  - antisense RNA, ribozyme RNA or any RNA or DNA which inhibits or prevents the expression of undesired protein/s in said mammalian cell; and
- optionally further comprising operatively linked regulatory elements sufficient for the expression and/or replication of said exogenous protein  
20 in a mammalian cell.
2. A construct according to claim 1 optionally further comprising additional SV40 protein or proteins, preferably SV40 agnoprotein.

3. A construct according to claim 1 or claim 2 comprising a mixture of at least two semi-purified or pure SV40 capsid proteins.
4. A construct according to any one of claims 1 to 3 comprising a mixture of three semi-purified or pure SV40 capsid proteins.
5. A construct according to claim 1 to 4 wherein said SV40 capsid protein is semi-purified or pure VP1 or VP2 or VP3.
6. A construct according to any one of claims 1 to 5 wherein said constituent is exogenous circular or linear DNA encoding an exogenous protein or peptide product, or itself a therapeutic product, or encoding therapeutic RNA, or a vector comprising exogenous DNA encoding therapeutic RNA or encoding an exogenous protein or peptide product.
7. A construct according to claim 6 wherein said DNA is DNA which encodes a therapeutic protein or peptide product which is not made or contained in said cell, or is DNA which encodes a therapeutic protein or peptide product which is made or contained in said cell in abnormally low amount, or is DNA which encodes a therapeutic protein or peptide product which is made or contained in said cell in defective form or is DNA which encodes a therapeutic protein or peptide product which is made or contained in said cell in physiologically abnormal or normal amount, or encodes a therapeutic RNA.
8. A construct according to claim 6 or claim 7 wherein said therapeutic protein or peptide product is an enzyme, a receptor, a structural protein, a regulatory protein or a hormone.
9. A construct according to any one of claims 6 to 8 comprising SV40-derived *ori* DNA sequence as a replication regulatory element and further comprising a DNA sequence encoding one or more regulatory elements sufficient for the

expression of said exogenous RNA or exogenous protein or peptide in said mammalian cell.

10. A construct according to any one of claims 1 to 5 wherein said constituent is exogenous RNA, wherein said RNA is RNA which encodes a therapeutic protein or peptide product which is not made or contained in said cell, or is RNA which encodes a therapeutic protein or peptide product which is made or contained in said cell in abnormally low amount, or is RNA which encodes a therapeutic protein or peptide product which is made contained in said cell in defective form, or is RNA which encodes a therapeutic protein or peptide product which is made or contained in said cell in physiologically abnormal or normal amount, said RNA having regulatory elements, including translation signal/s sufficient for the translation of said protein or peptide product in said mammalian cell, operatively linked thereto.
11. A construct according to claim 10 wherein said therapeutic protein or peptide product is an enzyme, a receptor, a structural protein, a regulatory protein or a hormone.
12. A construct according to any one of claims 1 to 5 wherein said constituent is an exogenous protein or peptide product.
13. A construct according to claim 12 wherein said protein or peptide product is, respectively, a therapeutic protein or peptide product which is not made or contained in said cell, or is a therapeutic protein or peptide product which is made or contained in said cell in abnormally low amount, or is a therapeutic protein or peptide product which is made or contained in said cell in defective form or is a therapeutic protein or peptide product which is made or contained in said cell in physiologically abnormal or normal amount.
14. A construct according to any one of claims 1 to 5 wherein said constituent is antisense RNA or DNA or ribozyme RNA, or any RNA or DNA which

inhibits or prevents the expression of undesired protein/s in said mammalian cell.

15. A construct according to claim 14 wherein said antisense RNA is antisense RNA directed against the *bcr/abl* transcript.

5 16. A construct according to claim 14 wherein said antisense RNA is antisense RNA directed against a HIV transcript.

17. A construct according to any one of the preceding claims wherein said cell is a human cell selected from the group consisting of hemopoietic cells, epithelial cells, endothelial cells, liver cells, epidermal cells, muscle cells, tumor cells, nerve cells and germ line cells.

18. A construct according to claim 17 wherein said hemopoietic cells are bone marrow cells, peripheral blood cells and cord blood cells, or liver cells.

19. A method for the *in vitro* construction of SV40 viruses or pseudoviruses comprising exogenous nucleic acid comprising the following steps:

15 a. bringing a semi-purified or pure SV40 capsid protein or a mixture of at least two such proteins into contact with said exogenous nucleic acid to give recombinant SV40 viruses or with a vector comprising said exogenous nucleic acid to give pseudoviruses; and

20 b. optionally subjecting the SV40 viruses or pseudoviruses formed in step (a) to digestion by nuclease to remove non-packaged DNA.

20. A method according to claim 19 wherein in step (a) at least one other SV40 protein, preferably SV40 agnoprotein, is added to the mixture of said SV40 capsid protein/s and said nucleic acid.

25 21. A method according to claim 19 or claim 20 wherein said SV40 capsid protein is semi-purified or pure SV40 VP1, VP2, or VP3.

22. A method according to any one of claims 19 to 21 wherein said exogenous nucleic acid is circular or linear DNA.
23. A method according to any one of claims 19 to 21 wherein said exogenous nucleic acid is RNA.
- 5 24. A method according to any one of claims 19 to 23 wherein said exogenous nucleic acid encodes a therapeutic protein or peptide product or itself a therapeutic product.
- 10 25. A method according to claim 22 wherein said DNA is DNA which encodes a therapeutic protein or peptide product which is not made or contained in said cell, or is DNA which encodes a therapeutic protein or peptide product which is made or contained in said cell in abnormally low amount, or is DNA which encodes a therapeutic protein or peptide product which is made or contained in said cell in defective form or is DNA which encodes a therapeutic protein or peptide product which is made or contained in said cell in physiologically abnormal or normal amount or is DNA which encodes a therapeutic RNA.
- 15 26. A method according to claim 25 wherein said exogenous DNA encodes a therapeutic protein or peptide product which is an enzyme, a receptor, a structural protein, a regulatory protein or a hormone.
- 20 27. A method according to claim 19 or claim 20 wherein in step (a) SV40-derived *ori* DNA sequence is added and said exogenous nucleic acid optionally has DNA sequence encoding one or more regulatory elements sufficient for the expression of said exogenous protein in said mammalian cell operatively linked thereto.
- 25 28. A method according to claims 19 or claim 20 wherein said nucleic acid is exogenous RNA, wherein said RNA is RNA which encodes a therapeutic protein or peptide product which is not made or contained in said cell, or is

RNA which encodes a therapeutic protein or peptide product which is made or contained in said cell in abnormally low amount, or is RNA which encodes a therapeutic protein or peptide product which is made or contained in said cell in defective form or is RNA which encodes a therapeutic protein or peptide product which is made or contained in said cell in physiologically abnormal or normal amount and wherein said RNA has regulatory elements, including translation signal, sufficient for the translation of said protein product in said mammalian cell, operatively linked thereto.

29. A method for *in vitro* construction of recombinant SV40 viruses or pseudoviruses comprising an exogenous protein or peptide comprising the following steps:

- a. bringing a semi-purified or purified SV40 capsid protein or a mixture of at least two such proteins into contact with said exogenous protein to give recombinant SV40 viruses or pseudoviruses; and
- b. optionally purifying the recombinant viruses or pseudoviruses obtained in step (a) from any non-packaged protein.

30. A method according to claim 29 wherein said exogenous protein or peptide are, respectively, a naturally occurring or recombinant protein or peptide, a chemically modified or peptide, or a synthetic protein or peptide.

31. A method according to claim 30 wherein said exogenous protein or peptide product are, respectively, a therapeutic protein or peptide product not made or contained in said cell, or are a therapeutic protein or peptide product made or contained in said cell in abnormally low amount, or are a therapeutic protein or peptide product made or contained in said cell in defective form or are a therapeutic protein or peptide product made or contained in said cell in physiologically abnormal or normal amount.

32. A method according to any one of claims 19 to 31 wherein said cell is a human cell selected from the group consisting of hemopoietic cells, muscle cells, tumor cells, nerve cells and germ line cells.
33. A method according to claim 32 wherein said hemopoietic cells are bone marrow cells, peripheral blood cells and cord blood cells, or liver cells.
34. A method for the *in vitro* construction of SV40 pseudoviruses comprising exogenous antisense RNA, or ribozyme RNA or RNA or DNA which inhibits or prevents the expression of undesired protein/s in a mammalian cell, comprising the following steps:
- a. bringing a semi-purified or pure SV40 capsid protein or a mixture of at least two such proteins into contact with said exogenous antisense RNA, or ribozyme RNA, or RNA or DNA which inhibits or prevents the expression of undesired protein/s in a mammalian cell, to give recombinant SV40 pseudoviruses; and
  - b. optionally subjecting the SV40 pseudoviruses formed in step (a) to digestion by nuclease to remove non-packaged DNA.
35. A method according to claim 32 wherein in step (a) at least one other SV40 protein, preferably SV40 agnoprotein, is added to the mixture of SV40 capsid protein/s and the exogenous nucleic acid or antisense nucleic acid.
36. A method according to claim 34 or claim 35 wherein said SV40 capsid protein is semi-purified or pure SV40 VP1, VP2, or VP3.
37. A method according to any one of claims 34 to 36 wherein said antisense RNA is antisense RNA directed against the *bcr/abl* transcript.
38. A method according to any one of claims 34 to 36 wherein said antisense RNA is antisense RNA directed against a HIV transcript.

39. A mammalian cell infected with a construct of any one of claims 1 to 18.

40. An infected human cell according to claim 39 selected from the group consisting of hemopoietic cells, muscle cells, tumor cells, nerve cells and germ line cells.

5 41. A mammalian cell infected with a construct obtained by the method of any one of claim 17 to 38.

42. An infected human cell according to claim 41 selected from the group consisting of hemopoietic cells, muscle cells, tumor cells, nerve cells and germ line cells.

10 43. A method of providing a therapeutic DNA, RNA, antisense RNA, ribozyme RNA, protein or peptide product to a patient in need of such product by administering to said patient a therapeutically effective amount of the SV40 viruses or pseudoviruses according to any one of claims 1 to 18.

15 44. A method of providing a therapeutic DNA, RNA, antisense RNA, ribozyme RNA, protein or peptide product to a patient in need of such product by administering to said patient a therapeutically effective amount of infected cells according to any one of claims 39 to 42.

20 45. Pharmaceutical compositions comprising as active ingredient a therapeutically effective amount of the SV40 viruses or pseudoviruses according to any one of claims 1 to 18.

46. Pharmaceutically compositions comprising as active ingredient a therapeutically effective amount of infected cells according to any one of claims 39 to claim 42.

## PATENT COOPERATION TREATY

## PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference <b>3/130/63-PCT</b>	<b>FOR FURTHER ACTION</b> see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. <b>PCT/IL 96/00143</b>	International filing date (day/month/year) <b>06/11/1996</b>	(Earliest) Priority Date (day/month/year) <b>06/11/1995</b>
Applicant <b>YISSUM RESEARCH DEVELOPMENT COMPANY OF .. et al.</b>		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. ☒ Certain claims were found unsearchable (see Box I).

2. ☐ Unity of invention is lacking (see Box II).

3. ☐ The international application contains disclosure of a nucleotide and/or amino acid sequence listing and the international search was carried out on the basis of the sequence listing

☐ filed with the international application.

☐ furnished by the applicant separately from the international application,

☐ but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.

☐ Transcribed by this Authority

4. With regard to the title, ☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the abstract,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this International Search Report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is:

Figure No. \_\_\_\_\_ ☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☒ None of the figures.

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: **43,44**  
because they relate to subject matter not required to be searched by this Authority, namely:  
**Remark: Although claims 43,44 (as far as in vivo methods are concerned) are directed to a method of treatment of (diagnostic method practised on) the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.**
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

## INTERNATIONAL SEARCH REPORT

International Application No  
PCT/IL 96/00143

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C12N15/86 C12N15/87 C12N15/37 C12N7/04 C12N5/10  
C07K14/025 A61K39/12 A61K48/00

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07K C12N A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JOURNAL OF VIROLOGY, vol. 67, no. 5, May 1993, pages 2779-2788, XP000645492 COLOMAR M. ET AL.: "Opening and refolding of Simian Virus 40 and in vitro packaging of foreign DNA" cited in the application see the whole document ---	1-6, 19-22, 39,41
X	WO 92 16638 A (PRIME 3 PRIME INC 5) 1 October 1992  see the whole document --- -/-	1-8,12, 13, 17-22, 24-26, 29,33, 39,41, 43-46



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

## \* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

14 March 1997

Date of mailing of the international search report

27.03.97

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Kania, T

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	HUMAN GENE THERAPY, vol. 6, no. 3, March 1995, pages 297-306, XP000645479 FORSTOVA, J. ET AL.: "Polyoma virus pseudocapsids as efficient carriers of heterologous DNA into mammalian cells" cited in the application see the whole document ---	1-46
A	PNAS, U.S.A., vol. 83, September 1986, pages 6925-6929, XP002027487 OPPENHEIM A. ET AL.: "Efficient introduction of plasmid DNA into human hemopoietic cells by encapsidation in Simian Virus 40 pseudovirions" cited in the application see the whole document ---	1-46
A	VIROLOGY, vol. 207, no. 1, 20 February 1995, pages 251-254, XP002027488 GHARAKHANIAN E. ET AL.: "SV40 VP1 assembles into disulfide-linked postpentameric complexes in cell-free lysates" see the whole document ---	1-46
A	SCIENCE, vol. 253, 2 August 1991, pages 562-565, XP002027489 SZCZYLIK C. ET AL.: "Selective inhibition of leukemia cell proliferation by bcr-abl antisense oligodeoxynucleotides" cited in the application see the whole document ---	15,37
T	BLOOD, vol. 88, no. 10, 15 November 1996, page 3903 XP000647476 SANDALON Z. ET AL.: "In vitro packaging of SV40 virions and pseudovirions: vector development for somatic gene therapy" see the whole document -----	1-46

### Innovation on patent family members

● T/IL 96/00143

Form PCT/ISA/210 (patent family annex) (July 1992)